Intradialytic Hypertension

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Agenda

- Introduction
- Definition of IDH
- Prevalence of IDH
- Clinical Characteristics
- Pathophysiologic Mechanisms
- Prognosis of IDH
- Treatment of IDH
- Conclusions

Introduction

- Hemodialysis is a life-sustaining procedure for end-stage kidney disease patients, but an accepted consequence of hemodialysis is the tendency for blood pressure to change frequently both during and between hemodialysis treatments.

- Large variability in BP measurements during hemodialysis is a risk factor for increased mortality in end-stage kidney disease patients.

- The adverse outcomes associated with large **decreases** in BP during HD are well known, but nephrologists should be aware of the clinical significance of **increases** in BP during hemodialysis, as well.

Introduction

- **Intradialytic hypertension** is an increase in BP from pre- to post-hemodialysis that has been shown to be associated with poor outcomes.
- Many nephrologists have been paged during calls by dialysis nurses because one of their patients was presenting with severe hypertension at the time of dialysis disconnection.
- IDH has been called paradoxical hypertension because it occurs during ultrafiltration.
- IDH often happens in patients starting the dialysis treatment (incident patients) but is also seen in patients treated for months or years with dialysis (prevalent patients).
- IDH occurs in 5% to 15% of treatments.

Definition of Hypertension

K/DOQI 2005 guidelines on cardiovascular disease in dialysis patients

Predialysis and postdialysis blood pressure goals should be <140/90mmHg and <130/80mmHg respectively (C)

Definition of IDH

- It can be defined as a sustained increase of blood pressure during the dialysis session with BP values during and at the end of the dialysis session exceeding BP values at dialysis onset.
- It may also happen when the predialysis BP is high and then becomes even higher during the usual hourly BP check and at the dialysis disconnection.
- Increase in BP that is resistant to ultrafiltration. This BP rise may be very severe with an impressive hypertension crisis.
- It is not necessary to frame this definition with strict numbers.
- There is **no** uniform definition of Intradialytic hypertension.

Definition

Definitions of IDH from clinical studies and reviews

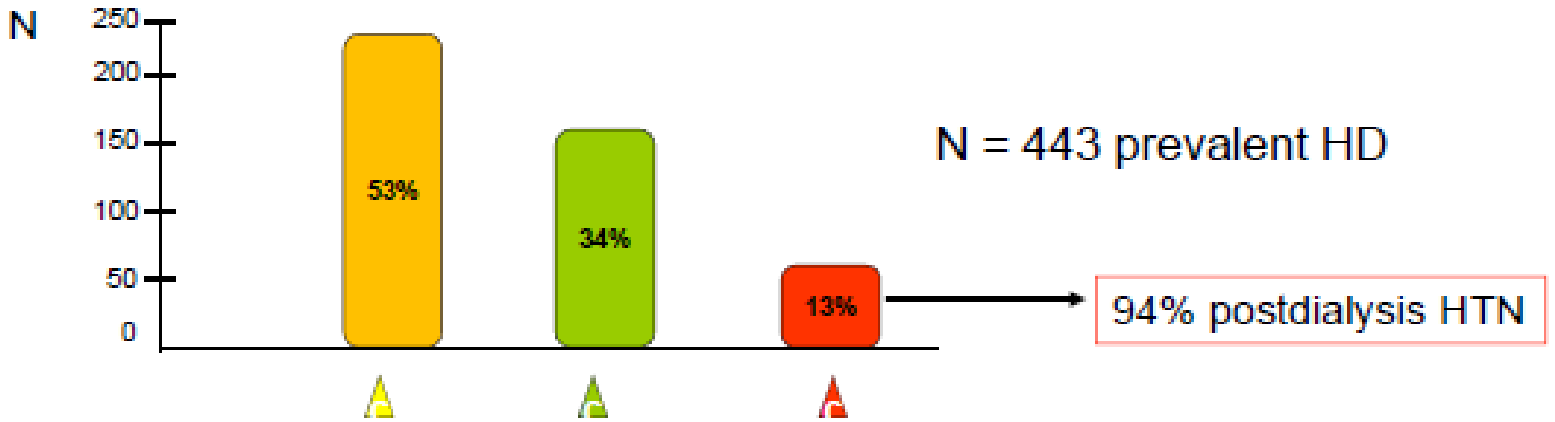
Reference	Definitions of IDH
Amerling et al. [5]	15-mm Hg increase of mean arterial pressure between the start and the end of the dialysis session

NB: low, normal or high predialysis BP

Chazot , Nephron Clin Pract 2010

Prevalence of IDH

CRIT-Line Intradialytic Monitoring Benefit (CLIMB) study



Inrig et al, Kidney Int, 2007

Clinical Characteristics

DMMS Wave 2 Study

- SBP ↓ ≥10 mm Hg (N = 744)
- Unchanged SBP (N = 791)
- SBP >10 mm Hg (N = 213)

Inrig et al Am J Kidney Dis 2009

Pathophysiologic Mechanisms

Potential Pathophysiologic Mechanisms of Intradialytic Hypertension

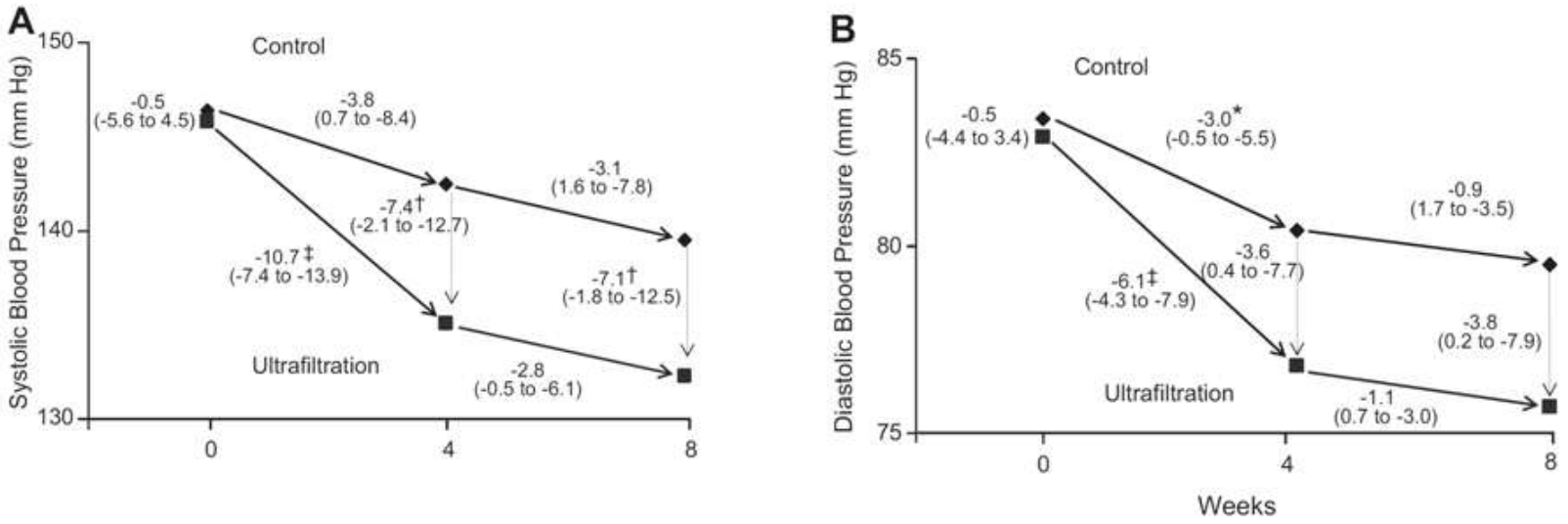
- Volume overload
- Sympathetic overactivity
- Activation of the renin-angiotensin-aldosterone system
- Endothelial cell dysfunction
- Dialysis-specific factors
  - Net sodium gain
  - High ionized calcium
  - Hypokalemia
- Medications
  - Erythropoietin-stimulating agents
  - Removal of antihypertensive medications
- Vascular stiffness

Inrig, Am J Kidney Dis 2009

Volume overload

- Volume expansion is the major factor in the development of HTN in dialysis patients.
- It leads to an elevation in BP via the rise in cardiac output and an inappropriately high systemic vascular resistance that may result from activation of the renin-angiotensin system or from the secretion of ouabain-like inhibitors of Na-K-ATPase, leading to elevations in intracellular sodium and calcium (The rise in cell calcium induce vasoconstriction).
- Attainment of "dry weight" can result in the normalization of BP in **> 60 %** of HD-dependent patients.
- The degree of extracellular volume expansion may be insufficient to induce edema; thus, the absence of edema does not exclude hypervolemia.

The effect of dry weight reduction on interdialytic ambulatory systolic and diastolic BP in hypertensive hemodialysis pts.



Agarwal et al. Hypertension 2009; 53: 500-507

Physiological changes during hemodialysis in patients with intradialysis hypertension

Table 2 | Laboratory data before and after hemodialysis

	Hypertension prone	Controls	*P*-value
Before hemodialysis			
Plasma potassium (mEq/l)	4.4 ± 0.3	4.4 ± 0.5	NS
Plasma free calcium (mg/dl)	4.2 ± 0.1	4.4 ± 0.1	NS
Plasma epinephrine (pg/ml)	97.1 ± 13.5	99.0 ± 8.5	NS
Plasma norepinephrine (pg/ml)	225 ± 43	253 ± 47	NS
Plasma renin concentration (pg/ml)	10.8 ± 3.4	15..1 ± 3.1	NS
After hemodialysis			
Plasma potassium (mEq/l)	3.2 ± 0.1*	3.3 ± 0.1*	NS
Plasma free calcium (mg/dl)	5.0 ± 0.1*	5.1 ± 0.1*	NS
Plasma epinephrine (pg/ml)	87.6 ± 9.8	100.4 ± 6.8	NS
Plasma norepinephrine (pg/ml)	204 ± 27	363 ± 62*	<0.05
Plasma renin concentration (pg/ml)	10.6 ± 2.8	24.9 ± 7.3*	<0.05

Kidney International (2006) 69, 1833–1838

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Kidney International (2006) 69, 1833–1838

Endothelial Cell Dysfunction

Table 4 | Plasma concentrations of nitric oxide (nitrate+nitrite) and endothelin (ET-1) before and after hemodialysis

	Hypertension prone	Control	*P*-value
Before hemodialysis			
NO (μM)	41.2 ± 6.1	32.9 ± 4.5	NS
ET-1 (pg/ml)	345.6 ± 34.5	287.4 ± 29.3	NS
NO/ET-1	0.869 ± 0.502	0.129 ± 0.013	NS
After hemodialysis			
NO (μM)	7.2 ± 0.9**	7.9 ± 0.9**	NS
ET-1 (pg/ml)	510.9 ± 43.3**	276.7 ± 30.1	< 0.05
NO/ET-1	0.018 ± 0.003**	0.034 ± 0.005**	< 0.05

Abbreviations: NO, nitric oxide; ET-1, endothelin; NS, not significant.
All data are presented as mean ± s.e.m.
*$P < 0.05$ when compared with values before hemodialysis, **$P < 0.005$ when compared with values before hemodialysis.

Chou, et al Kidney Int 2006

Net Sodium gain

- In HD patients, the sodium balance becomes positive when dietary sodium intake exceeds sodium removal during dialysis and a low sodium diet should be advised in most dialysis patients.
- Although a high sodium concentration in dialysate has been used to improve dialysis tolerance, it increases sodium diffusion (Intradialytic sodium gain) and exposes the patient to a high intradialytic BP.
- **Oberleithner et al;** demonstrated a dramatic and rapid stiffening effect of cultured endothelial cells in a high sodium concentration medium that was associated with NO synthesis down-regulation.
- Sodium appears as the culprit for IDH.

Potassium – Calcium

- Hypokaliemia: direct vasoconstrictor effect
- Acute increase Ca^{++}: increases myocardial contractility and cardiac output

Pre/Post (plasma)	IDH group	Control group	p value between groups
K^+	↓	↓	NS
Ca^{2+}	↑	↑	NS

Chou et al Kidney int 2006

Summary of pre/post variations of biochemical/endocrine markers in IDH patients and in controls in the study by Chou et al. [4]

Pre/Post (plasma)	IDH group	Control group	p value between groups
Epinephrine	↔	↔	NS
Norepinephrine	↔	↑	<0.05
Renin	↔	↑	<0.05
Endothelin	↑	↔	<0.05
K^+	↓	↓	NS
Ca^{2+}	↑	↑	NS

Erythropoietin- stimulating agents

- An increase in BP of 10 mmHg or more may occur in patients with renal failure who are treated with erythropoietin.
- The risk is greatest in those with rapid correction of severe anemia and with preexistent hypertension.

- Intravenous administration of rHuEPO has been associated with elevations in blood pressure in dialysis patients and interestingly also with elevations in endothelin-1.
- Changing the administration of rHuEPO from the intravenous to the subcutaneous route has been associated with improved blood pressure control in hypertensive dialysis patients.

Removal of antihypertensive medications

- Many blood pressure lowering medications including B-blockers and ACE inhibitors are significantly removed during dialysis.
- Removal of these agents is a potential contributor in some cases.

Antihypertensive medications

β-Blockers and combined α- and β-blockers			
Acebutolol	~ 120 hours	25–30 mg q48	75%
Metoprolol	3–8 hours	50–200 mg bid	High
Metoprolol XL	?	50–400 mg qd	High
Propranolol	3–6 hours	40–120 mg bid	< 5%
Carvedilol	7–10 hours	6.25–25 mg bid	None
Carvedilol CR	?	20–80 mg qd	None
Labetalol	6–8 hours	100–1200 mg bid	< 1%
Calcium channel blockers			
Amlodipine	?	2.5–10 mg qd	None
Diltiazem	Prolonged	Varies with formulation	< 30%
Nifedipine	~5 hours	30–180 mg qd[a]	Low
Nicardipine	Prolonged	30–90 mg bid[a]	?
Felodipine	11–16	2.5–10 mg qd[a]	No
Verapamil	Prolonged	Varies with formulation	Low
Alpha-adrenergic blockers			
Doxazosin[c]	15–22 hours	1–8 mg qhs	None
Terazosin	9–12 hours	1–20 mg qhs	None
Prazosin	2–4 hours	1–5 mg bid to tid	?
Other			
Clonidine	18–41 hours	0.1–0.4 mg bid-tid	< 5%
Hydralazine	7–16 hours	10–100 mg q8 hour	None
Isosorbide dinitrate	?	5–40 mg tid	Yes
Minoxidil	?	5–100 mg qd	Partially

Qd, every day; bid, twice a day; tid, three times a day; qhs, at bedtime.
[a]Not recommended with crcl < 30 ml/min and contraindicated in anuric patients.
[b]Contraindicated with crcl < 30 ml/min.
[c]Extended release formulations.

Pharmacokinetic properties of ARB's in ESRD

	T1/2(h) normal	T1/2(h) ESRD	Initial dose in HD	Maintenance dose in HD	Removal during HD
Candesartan	9	?	4 q24h	8-32 q24h	No
Irbesartan	11-15	11-15	75-150 q24h	150-300 q24h	No
Losartan	2	4	50 q24h	50-100 q24h	No
Telmisartan	24	?	40 q24h	20-80 q24h	No
Valsartan	6	?	80 q24h	80-160 q24h	No

Henrich W. Principles and Practice of Dialysis

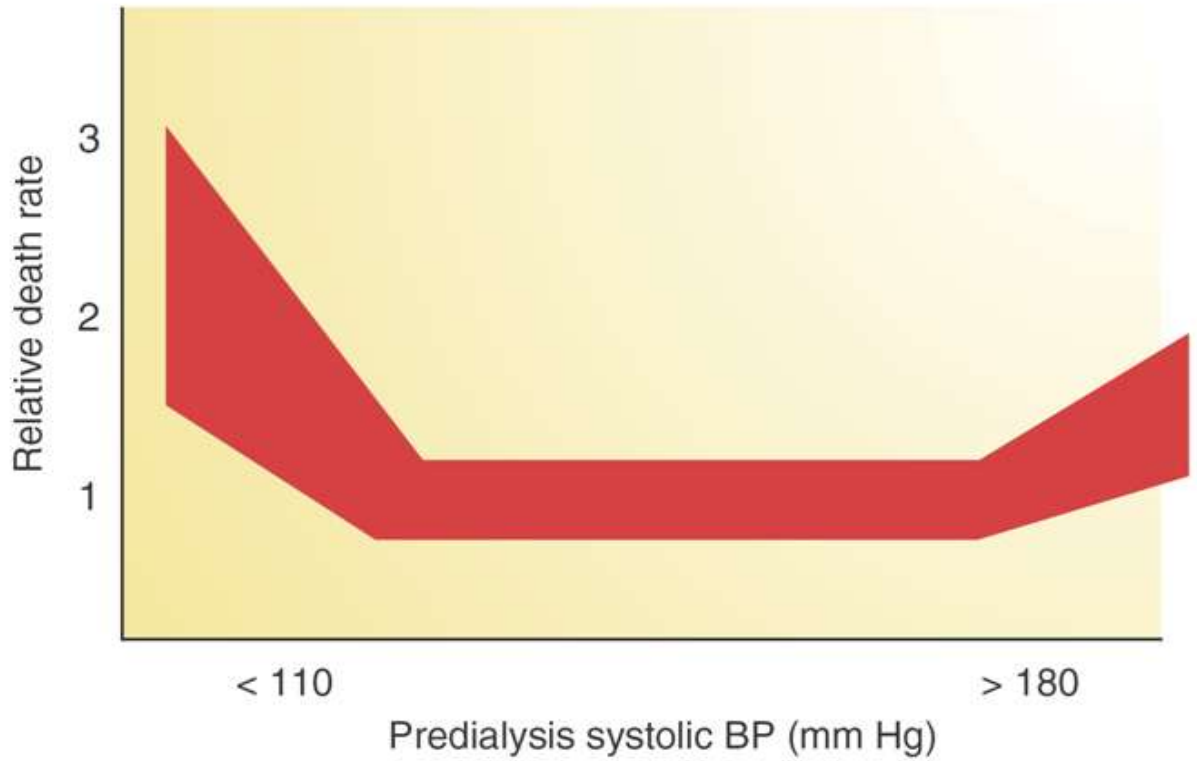
Arterial stiffness

- Arterial stiffness, measured by pulse wave velocity.
- Pulse wave velocity was higher in patients with HD-unresponsive BP (12.9 vs. 10.8 m/s), suggesting unrecognized arteriosclerosis to either contribute to the occurrence of intradialytic hypertension or to be its consequence.
    - Mourad ., et al. *Nephrology (Carlton)* 2005;10:438–441

Prognosis of IDH

- In one study, an increase in arterial BP during dialysis was associated with an increased risk of hospitalization or death at 6 months when compared to a decrease in BP during dialysis.
- Time-averaged blood pressure measurements correlate better with postdialysis than with predialysis blood pressure, and dialysis patients often fail to show the normal “nocturnal dip” in blood pressure.
- Elevated postdialysis pulse pressure was associated with a 12% increase in the hazard for death.

Relationship between blood pressure and mortality in dialysis patients.



Luther JM Kidn Int 2008;73:667-668

Postdialysis blood pressure rise predicts long-term outcomes in chronic hemodialysis patients: a four-year prospective observational cohort study

Background

The blood pressure (BP) of a proportion of chronic hemodialysis (HD) patients rises after HD. We investigated the influence of postdialysis BP rise on long-term outcomes.

Methods

A total of **115** prevalent HD patients were enrolled. Because of the fluctuating nature of predialysis and postdialysis BP, systolic BP (SBP) and diastolic BP (DBP) before and after HD were recorded from **25** consecutive HD sessions during a **2-**month period. Patients were followed for **4** years or until death or withdrawal.

Results

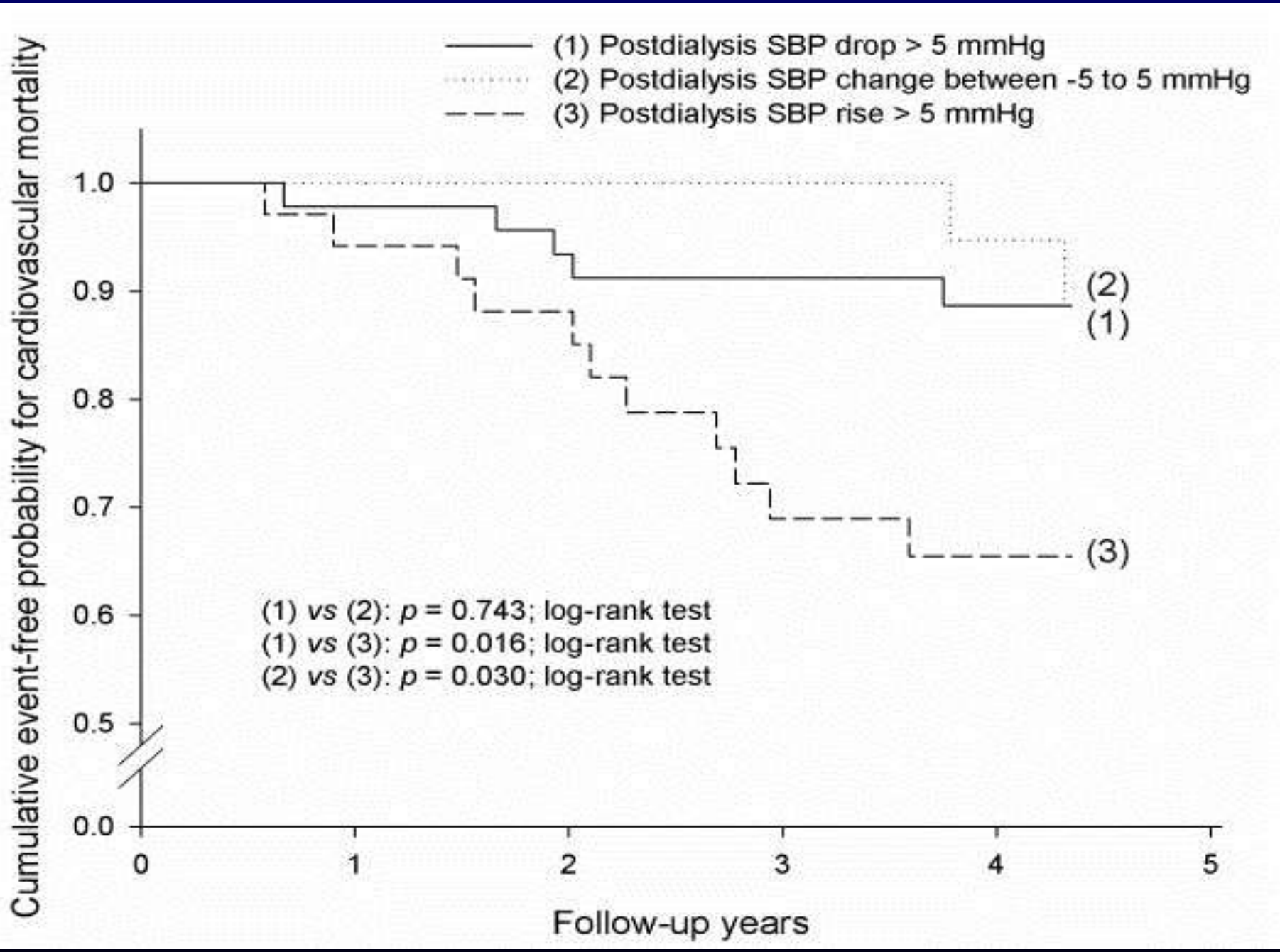
Kaplan-Meier estimates revealed that patients with average postdialysis SBP rise of **> 5** mmHg were at the highest risk of both cardiovascular and all-cause mortality as compared to those with an average postdialysis SBP change between **- 5 to 5** mmHg and those with an average postdialysis SBP drop of **> 5** mmHg.

Furthermore, multivariate Cox regression analysis indicated that both postdialysis SBP rise of **>** 5 mmHg (HR, 3.925 [95% CI, 1.410-10.846], $p = 0.008$) and high cardiothoracic (CT) ratio of **>** 50% (HR, 7.560 [95% CI, 2.048-27.912], $p = 0.002$) independently predicted all-cause mortality.

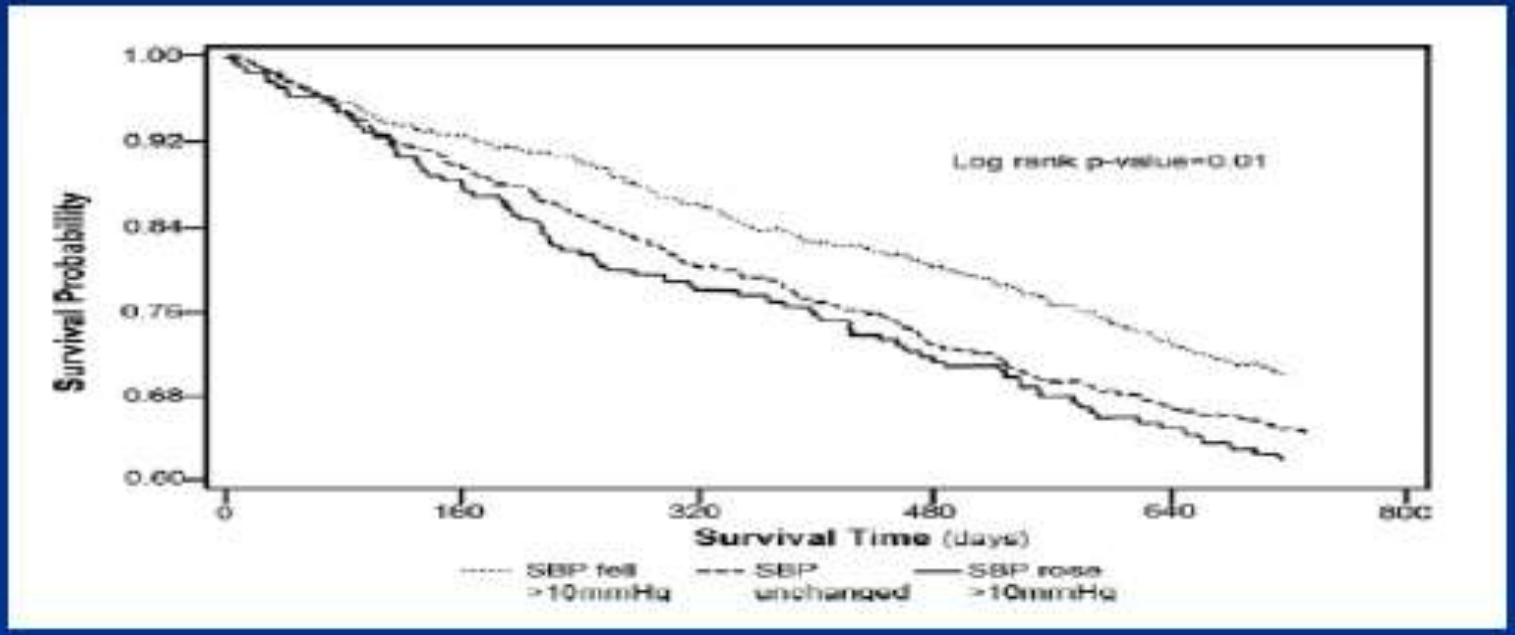
We also found that patients with an average postdialysis SBP rise were associated with subclinical volume overload, as evidenced by the significantly higher CT ratio ($p = 0.008$).

Conclusions

A postdialysis SBP rise in HD patients independently predicted 4-year cardiovascular and all-cause mortality. Considering postdialysis SBP rise was associated with higher CT ratio, intensive evaluation of cardiac and volume status should be performed in patients with postdialysis SBP rise.


(1) Postdialysis SBP drop > 5 mmHg
(2) Postdialysis SBP change between -5 to 5 mmHg
(3) Postdialysis SBP rise > 5 mmHg
Cumulative event-free probability for cardiovascular mortality
1.0
0.9
0.8
0.7
0.6
0.5
0.0
0
1
2
3
4
5
Follow-up years
(2)
(1)
(3)
(1) vs (2): p = 0.743; log-rank test
(1) vs (3): p = 0.016; log-rank test
(2) vs (3): p = 0.030; log-rank test

Association of Blood Pressure Increases During Hemodialysis With 2-Year Mortality in Incident Hemodialysis Patients: A Secondary Analysis of the Dialysis Morbidity and Mortality Wave 2 Study



	SBP Decreased > 10 mm Hg During HD (n = 744)	SBP Unchanged ±10 mm Hg During HD (n = 791)	SBP Increased > 10 mm Hg During HD (n = 213)
2-Year all-cause mortality	218 (29.3)	273 (34.5)	79 (37.1)
Cardiovascular related*	126 (57.8)	161 (59.0)	49 (62.0)

American Journal of Kidney Diseases, Vol 54, No 5 (November), 2009: pp 881-890

Potential strategies for the treatment of intradialytic hypertension

Table 1 | Potential strategies for the treatment of intradialytic hypertension

Potential strategy	Potential methods
Reduce volume overload	Increase ultrafiltration Reduce cardiac output Restrict dietary salt

Locatelli et al Nat. Rev. Nephrol. 2009

Treatment of IDH

- First, Lifestyle modifications such as weight reduction, dietary modification, sodium restriction, physical activity and smoking cessation can reduce systolic blood pressure from 2-14 mm Hg.
- Dry-weight reduction is to be considered as an initial approach in any hypertensive hemodialysis patient.
- Fluid removal, the amount of removed fluid was equivalent to 7.5–11% of the body weight in days or weeks. However, it must be done with caution to avoid hazardous BP drops that may occur in **elderly** or patients with severe comorbidity.
- Longer or more frequent dialysis may be necessary to avoid the UF side effects or hasten the amelioration of this complication.

Treatment of IDH

- Dialysis prescriptions should be tailored to achieve a net negative sodium solute balance. To have adequate sodium solute removal during hemodialysis.
- Limiting the use of high-calcium dialysate unless clinically indicated.
- As dry-weight reduction may not be sustainable or tolerable, pharmacologic antihypertensive therapy will be required in most hypertensive hemodialysis patients.
- Avoidance of dialyzable antihypertensive medications.
- **Avoid routine withholding of BP medications prior to hemodialysis.**

Treatment of IDH

- Inhibition of the sympathetic nervous system. In particular, carvedilol and labetolol with combined alpha and beta-adrenergic blockade should be considered as they are not significantly removed by hemodialysis.
- Inhibit the renin angiotensin aldosterone system.
- Use medication that decrease arterial stiffness.
- Reducing erythropoeitin dose in patients with severe hypertension.
- Nephrectomy in resistant cases.
- Renal transplantation or conversion to PD.

Treatment of IDH

- Specific ET1 antagonists (such as Avosentan) may be effective; further studies are required as regard its safety usage in hemodialysis patients.

- Selecting drugs that may have pleiotropic properties that specifically benefit intradialytic hypertension patients beyond overall lowering of BP should also be considered.
- Nonspecific ET1 inhibitors as Carvedilol, which blocks endothelin-1 release, appears to be effective in this setting.

Treatment of IDH

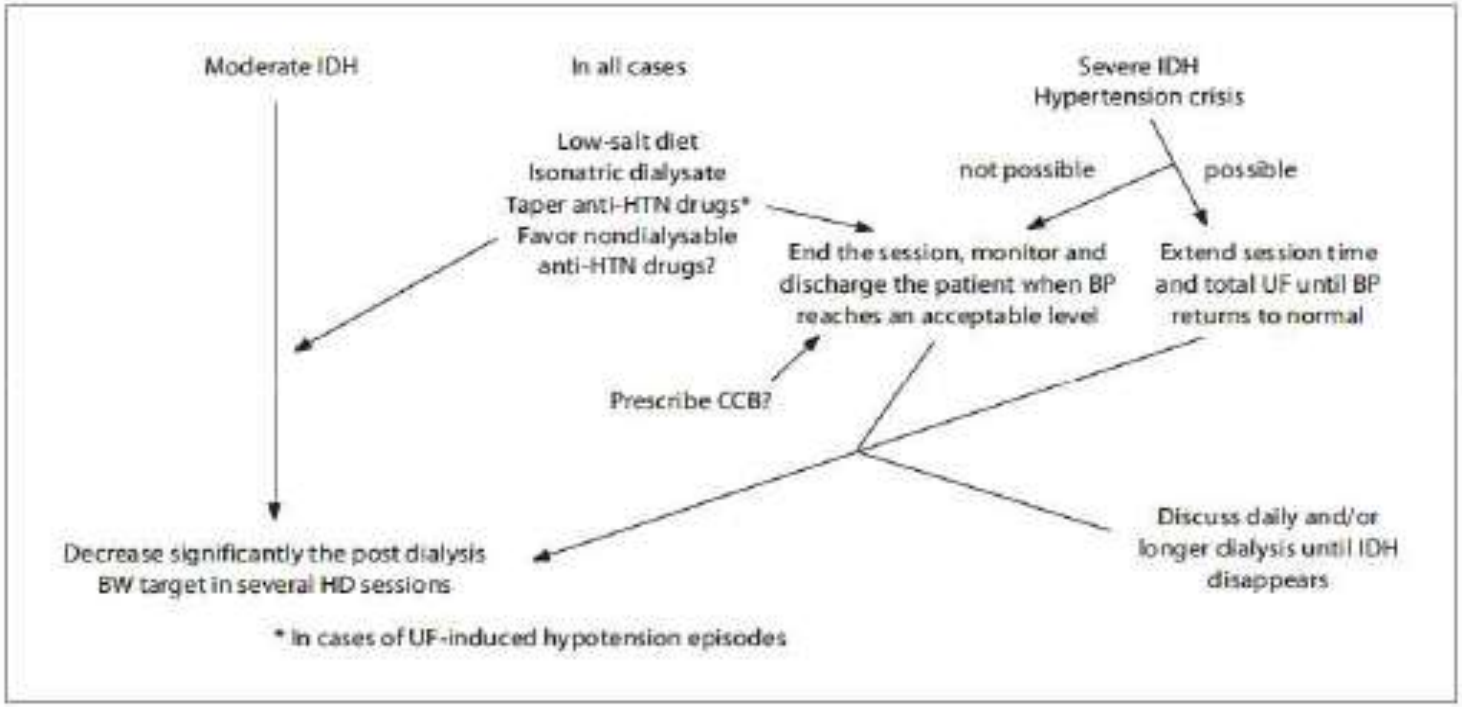


Fig. 3. Proposed algorithm to handle IDH according to its severity. Prescribing CCB in the case of severe IDH or favoring nondialyzable antihypertensive drugs appear to be opinion-based hypotheses and their effect on IDH has not been reported even in observational studies. BW = Body weight; CCB = calcium channel blockers; anti-HTN = antihypertensive.

Chazot, Nephron Clin Pract 2010

Conclusions

- Intradialytic hypertension is an under recognized marker of increased risk for morbidity and mortality among maintenance HD patients. IDH present in 5-15% of HD patients.
- IDH is an unusual expression of extracellular fluid overload. It is efficiently corrected by fluid removal. Careful attention to the optimal dry body weight.
- Endothelial cell dysfunction appears to be a major mechanism underlying this phenotype.
- Select antihypertensive medications according to the elimination profile and the use of receptor blockers.
- Improving our knowledge of this complication will contribute to decreasing the high burden of cardiovascular complications occurring in dialysis patients.

THANK YOU